REMARKS

Claims 1-15 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the amendments made herein and the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Rejection of Claims 14-15 Under 35 U.S.C. § 112, Second Paragraph

Claims 14-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The examiner cites the phrase "less than about" in pending Claims 14-15 as being vague and indefinite.

Applicants have amended Claims 14-15 to delete the word "about." Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-7 and- 9-15 Under 35 U.S.C. § 102(b) or § 103(a)

Claims 1-7 and 9-15 are rejected under 35 U.S.C. § 102(b) as anticipated by Winkler *et al.* (U.S. Patent No. 5,885,837, issued March 23rd 1999, Ref. A in Office Action of March 3rd 2004). The Examiner acknowledges that Winkler *et al.* is silent with regard to vertical positioning of the substrate/support. However, the Examiner asserts that the vertical position recited in Claim 1 is inherent in the flow through channels of Winkler *et al.* because Winkler *et al.* teach that the flow channels lead "up to the synthesis chamber" (Column 11, lines 42-43), which the Examiner believes suggests that the flow channels, and hence substrate, are vertically positioned.

Applicants respectfully traverse the rejection. As noted in MPEP § 2112, "'To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d, 1949, 1950-51 (Fed. Cir. 1999). Applicants assert that Winkler *et al.* do not teach or suggest all the limitations of the claimed method. In particular, the vertical positioning of the substrate is not inherent in the work of Winkler *et al.* Figs. 4a and 4b illustrate details of the first embodiment of a device,

which contains the substrate, used for performing the synthesis of arrays of diverse polymers as disclosed by Winkler *et al.* Notably, Fig. 4a is described as a "top view" and Fig. 4b as "a cross-sectional side view" of this device (Column 8, lines 9-15). Applicants submit that a "top view" is analogous to a "birds-eye view" or more specifically a view from above by which the viewer is viewing the object vertically downward. If the device, and hence substrate contained therein, were positioned vertically, then the "top view" would be identical to one of the "cross-sectional side views" of the device. This is not the case, as Winkler *et al.* clearly show in Fig. 4a and Fig. 4b that the "top view" and "cross-sectional side view" are different. Moreover, the only way the device, and hence the substrate therein, could have identical "cross-sectional side views" is if it were in a **horizontal** position. Applicants respectfully point out that according to the specification (Column 11, lines 30-32), Fig. 6b "illustrates the system in top view," where by one is looking vertically downward at the substrate. Clearly, the substrate is positioned **horizontally**; that is, the long axes of the substrate are parallel with the ground. Applicants assert that Winkler *et al.* implicitly teach a **horizontal** positioning of the substrate in view of Figs. 4a/4b and 6b.

The Examiner refers to Figs. 6a and 6b and states that the flow channels are illustrated as vertical (presumably in Fig. 6a) and hence that the substrate must then be positioned vertically since the flow channels lead "up to the synthesis chamber." The Examiner's argument assumes that if the flow channels are positioned vertically, then the substrate must also be positioned vertically. The specification recites that Fig. 6a illustrates "the system in end view cross-section," i.e., a view from the side, a view that is perpendicular to that displayed in Fig. 6b, where the substrate is shown to be horizontally positioned. As noted above, Figs. 4a/4b and 6b show a horizontal substrate positioning. Thus, if the flow path is vertical in Fig. 6a, as the Examiner has suggested, then it is evident from the fact that the "cross-section" in 6a is perpendicular to the "top view" of 6b, i.e., perpendicular to the horizontally positioned substrate, that the direction of flow path (vertical) need not coincide with the substrate positioning (horizontal). Accordingly, Applicants assert that, in regard to the use of microvalve structures as illustrated in Figs. 6a and 6b, the flow through channels described by Winkler *et al.* need **not** move in parallel with the plane made by the substrate; that is, if the flow channels do indeed mark a vertical path, the substrate need not be positioned vertically. As a result, it is not a requirement that a vertical flow path be synonymous with a vertical substrate positioning. Thus the Examiner's position that a vertical alignment of the flow channels makes a vertical substrate

alignment inherent is not supported since Figs. 6a and 6b teach that the flow channels are perpendicular to the substrate positioning.

Thus, the method taught by Winkler *et al.* does not teach a vertical positioning of the substrate, but rather a **horizontal** positioning. Additionally, a vertical flow channel positioning does not necessarily correspond to a vertical substrate positioning. While the Examiner believes that the vertical position recited in pending Claim 1 is inherent in the flow through channels of Winkler *et al.* because they teach that the flow channels "lead up to the synthesis chamber" (Column 11, lines 42-43), Applicants assert that different interpretations of the phrase "lead up to the synthesis chamber," such as "connect to the synthesis chamber" or "intersect the synthesis chamber," are more consistent with the invention described by Winkler *et al.*, especially in light of Figs. 6a and 6b. Hence, in view of the arguments and presented above, Applicants assert that vertical substrate positioning is not inherent in Winkler *et al.* and that the instant invention is not anticipated by Winkler *et al.* Applicants respectfully request reconsideration and withdrawal of the rejection.

In the alternative, claims 1-15 are rejected under 35 U.S.C. § 103(a) as obvious over Winkler *et al.* (U.S. Patent No. 5,885,837, issued March 23rd 1999). The Examiner states that it would have been obvious to one of ordinary skill in the art at the time to position the substrate comprising flow channels in a vertical position to provide for reagent flow through the channels via gravitational force. The Examiner states that reagent flow by gravitational force would eliminate "dead spots" cited as problematic by Winkler *et al.*

Applicants respectfully traverse the rejection. Pursuant to MPEP 2142:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants assert that there is no motivation to modify the method of Winkler *et al.* to include a vertical substrate positioning in order to eliminate "dead spots" because, as noted above, a vertical positioning of the substrate does not necessarily coincide with a vertical positioning of the flow channels as expressly taught by Winkler *et al.* in Figs. 6a and 6b. Furthermore, Winkler *et al.* teaches the use of flow channels that are not entirely vertical (e.g., horizontal, circular, serpentine; see Column 5, lines 27-31). In these non-vertical channels the force of gravity is expected to cause reagent flow to slow at horizontal segments of the flow channel and to stagnate in the nadirs of the flow channel. This buildup of different reagent concentrations at different points within the channels is directly proportional to the occurrence of "dead spots." Hence, using the force of gravity, as suggested by the Examiner, to promote reagent flow down a channel would in fact facilitate the formation of "dead spots" and may even render the device of Winkler *et al.* unsuitable for its intended purpose, especially when the channel paths are horizontal, circular, or serpentine. As stated in MPEP § 2143.01, "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." Accordingly, Applicants assert that, contrary to the Examiner's position, there is no motivation to modify the method of Winkler *et al.* to include a vertical substrate positioning to eliminate "dead spots" through reagent flow under the influence of gravity because a vertical substrate position would not necessarily coincide with a vertical channel flow and such a vertical position would not eliminate "dead spots."

Furthermore, although it is **not relevant** to the discussion of vertical substrate positioning since vertical substrate positioning is not synonymous with vertical channel flow, Applicants assert it would not have been obvious to one of ordinary skill in the art to modify the method of Winkler *et al.* to include a vertical channel flow positioning in order to eliminate "dead spots," as advanced by the Examiner, because there would have been no reasonable expectation of success. In particular, since dead spots are a result of lack of homogeneous reagent flow through the channel, the action of gravity to promote reagent flow would be expected to **increase** the occurrence of "dead spots" in the channel, particularly since the flow path of the reagents would be governed by the shortest vertical path, i.e., by gravity, since there is no force to compel regent flow to inhabit the entire volume of the channel. This is especially applicable to channels in the channel bloc that carve horizontal, circular, and serpentine paths, as disclosed by Winkler *et al.*

(Column 5, lines 27-31). Applicants assert there would have been no reasonable expectation of success in modifying the method of Winkler *et al.* to include vertical substrate positioning to minimize the occurrence of "dead spots," since one of ordinary skill in the art would recognize that such a combination would produce the opposite effect, i.e., a proliferation of "dead spots." Thus, Applicants assert that there would have been no reasonable expectation of success in modifying the method of Winkler *et al.* to include a vertical channel flow, to facilitate reagent flow through the force of gravity.

In contrast to Winkler *et al.*, Example 1 of the subject application demonstrates that rotation of the substrate within the vertical plane results in a support where the attached nucleic acid array has decreased intrasupport variability; in other words, the nucleic acid array is more uniform across the support. Winkler *et al.* provide no teachings related to the uniformity of a nucleic acid array. In particular, there is no teaching or suggestion that varying the rotational position of the support while in a vertical position among nucleotide attaching steps can decrease the variability of the array. In fact, Winkler *et al.* did not even recognize the problem of nucleic acid arrays having significant intrasupport variability. Prior to the present invention, one of ordinary skill in the art would have had no reason to believe that the recited type of rotation of a support in a vertical plane would produce a nucleic acid array having superior properties and would have had no motivation to modify the method of Winkler *et al.* to include rotation of the substrate while in a vertical position.

Thus, the claimed method would not have been obvious to one of ordinary skill in the art, as Winkler *et al.* provide no teaching or suggestion for one to carry out a nucleic acid array preparation method wherein the support is rotated while in a vertical position. Moreover, the subject application makes the surprising discovery that when a nucleic acid array is prepared by a method that includes rotating a vertically positioned substrate, the resulting nucleic acid array has less intrasupport variability. According to the MPEP § 716.02(c), "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). Hence, Applicants also assert that the present invention is not obvious over the method of Winkler *et al.* in light of the unexpected result of a decrease in the intrasupport variability of a nucleic acid array prepared by the same method.

Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner's comments with respect to dependent Claims 2-7 and 9-15 are not specifically addressed further in light of the above arguments supporting the patentability of independent Claim 1.

Rejection of Claims 1-15 Under 35 U.S.C. § 103(a)

Claims 1-7 and 9-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gamble *et al.* (U.S. Patent No. 5,981,733, issued November 9th 1999, Ref. A in Office Action of October 3rd 2002) in view of Winkler *et al.* (U.S. Patent No. 5,885,837, issued March 23rd 1999). The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the substrate/support rotation of Gamble *et al.* with the substrate/support rotation of Winkler *et al.* providing a different rotational position relative to the previous attachment/binding step.

The applicants respectfully traverse the rejection. The Examiner notes that Gamble *et al.* teach a method for nucleic acid array synthesis wherein the support has a different position relative to the support in the prior attaching step (i.e., moved along the X-Y axis, Column 12, lines 52-54) but does not teach the rotated position is different from a previous attachment/binding step. The Examiner further acknowledges that Winkler *et al.* describe a method for nucleic acid array synthesis wherein the support is rotated with said rotation being prior to, coincident with, or subsequent to either binding or attaching steps and wherein the support has a different rotational position relative to a previous step (Column, 15, lines 53-67). Applicants assert that there would be neither a motivation to combine the vertical substrate positioning taught by Gamble *et al.* with the rotational positioning of the substrate taught by Winkler *et al.* nor a reasonable expectation of success in light of the design limitations imposed by Gamble *et al.*

Specifically, the rotational positioning of the support in Gamble *et al.* is the same during each of the nucleotide addition steps. This is clearly illustrated in Fig. 7 of Gamble *et al.* Fig. 7 shows that in moving from the jetting device to the reaction chamber, the support is first rotated from horizontal to a vertical orientation, and then is rotated such that the longer dimension of the

support is oriented along the z-axis. The support is then returned to the exact same position for each of the nucleotide addition steps, despite the rotation between nucleotide addition steps. If the support were to be rotated such that it was at a different position relative to a previous step (as taught by Winkler *et al.*), it would not properly interact with the reaction chamber. The support must interact in a specific manner with the reaction chamber such that "the majority of the surface of the substrate in the reaction chamber cell is between the path of the reagent stream from the bottom port to the top port" (Column 7, lines 3-6). Since the reaction chamber, as depicted in Fig. 7, is in a fixed position within the device, the substrate must be in the same position each time it interacts with the reaction chamber, as depicted in Fig. 7. Deviation from this set position can cause inappropriate dispensing of the reagents to the support in the reaction chamber leading to spillage or inaccurate dispensing. Accuracy during reagent dispensing is a key feature of Gamble *et al.* (Column, 9, lines 20-23). Another potential problem resulting from deviation from the set substrate position is the inability to form a "sealed, environmentally controlled enclosure" within the reaction chamber, this latter being disclosed by Gamble *et al.* as important for synthesis of oligonucleotides using phosphoramidites (Column 3, lines 51-55 and Column 12, lines 21-26).

Since the method of Gamble *et al.* requires that the support be in the same position for each nucleotide attachment step, in order for "the majority of the surface of the substrate in the reaction chamber cell" to be "between the path of the reagent stream from the bottom port to the top port" and in order to maintain accuracy and a "sealed, environmentally controlled enclosure," one of ordinary skill in the art would not have been motivated to modify the teachings of Gamble *et al.* to incorporate rotational positioning as taught Winkler *et al.* since such a combination would preclude many of these beneficial features of the Gamble *et al.* invention.

Additionally, modification of Gamble *et al.* with the rotational positioning taught by Winkler *et al.* would change the principle of operation of the device of Gamble *et al*, since establishing different rotational positioning of the substrate from a previous attachment/binding step is not within the possibility of the design of the Gamble *et al.* device. Pursuant to MPEP § 2143.01, if a "proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious."

Furthermore, in view of the design limitations of Gamble *et al.*, one of ordinary skill in the art would have had no reasonable expectation of success, as required for an obviousness rejection (See MPEP § 2143.02), in combining the teachings of Gamble *et al.* with those of Winkler *et al.*

In view of the above arguments, Applicants assert that the instant invention is not rendered obvious by Gamble *et al.* in view of Winkler *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner's objections to dependent Claims 2-15 are not addressed in light of the above arguments supporting the independent Claim 1.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

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LMT

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